Title: Establishing Reevaluation Intervals for API Intermediates					
Guidance Number: 126					
Prepared by:		Date:		Supersedes:	
Checked by:		Date:		Date Issued:	
Approved by:		Date:		Review Date:	

Introduction:
This document provides guidance for establishing re-evaluation intervals for API Intermediates that are stored dry or wet in drums or intermediate bulk containers (IBC). Wet intermediates include solvent wet, water wet, intermediates in solution (liquid) and intermediates in suspension. API Intermediates for Sale require stability studies and are outside the scope of this guidance document. Intermediates for Biological Products are also out of scope of this document.

Practice:
This document is intended to provide risk based guidance for the determination of re-evaluation intervals for API Intermediates. For API Intermediates that have a higher risk for degradation or for the proliferation of microbial organisms, hold time studies or microbiological proliferation studies can be used to support the determination of re-evaluation intervals.

- **Dry intermediates or intermediates that are stored as oils** that are considered stable through appropriate scientific judgment or literature search, through experience during development activities, or through consistent historical data gathered during routine manufacturing can use the "one year" default re-evaluation interval.

- **Wet intermediates** (Intermediates in solution, suspension, or wet cake) have a greater risk than dry intermediates for chemical degradation and/or microbial contamination. Microbiological concern is reduced if the material is wet with, dissolved in or suspended in an organic solvent as it is generally accepted that organic solvents impede the proliferation of organisms. Appendix I and II list risk assessment information for determining a re-evaluation period for wet intermediates relative to potential microbial proliferation.

Discussion & Recommendations
Intermediates that are stored wet have a greater potential for chemical degradation. If these wet intermediates are stored refrigerated or stored under nitrogen the potential chemical degradation process can be slowed. To support a storage time beyond 3 months, hold time studies should be considered.

Since analytical test methods for the evaluation of intermediates are typically not stability indicating the primary method of assessing chemical degradation is to process the intermediate forward, monitor subsequent processing, and test the final API for impurities. This activity can be performed retrospectively or prospectively.

See Appendix III for guidance on intermediate hold time studies to test the impact of any potential chemical degradation on the final API. Also intermediates that are stored wet have a greater potential for the proliferation of microbiological organisms. In addition to the risk of these microorganisms moving forward into the final API and subsequent Drug Product, there is the potential risk of by-products associated with microbial growth (endotoxins, exotoxins and other metabolites) also ending up in the final Drug Product. In assessing the microbial risk of storing wet intermediates there are two key risk components to consider.

Appendix I

(Determination of a microbial proliferation *Risk Band* to help propose a reevaluation interval for wet intermediates)

Severity Factors for Microbial Proliferation (Risk Category One)

Factor	Description
1	Solid Oral Dosage, Powder for Oral Suspension, nonaqueous liquid Oral Dosage Product, nonaqueous liquid or semi-solid Topical Product
2	Aqueous Liquid Oral Dosage products, Aqueous liquid or semi-solid Topical Products, Otic Products, Ophthalmic Products, and Inhalant Products
3	Sterile Injectable Products

Probability Factors for Microbial Proliferation (Risk Category Two)

Factor	Description
1	Characteristics of the intermediate are not favorable for microbial proliferation (See Appendix II) - **no proliferation of bioload**
8*	Characteristics of the intermediate are favorable for microbial proliferation (See Appendix II **possible proliferation of bioload**

*Probability reduction considerations affecting intermediates stored in conditions favorable for microbial proliferation that can be subtracted from the factor "8" to lower the probability factor.

3	Intermediates stored at conditions (eg. refrigerated) not conducive to microbial proliferation - **bioload stabilized**
2	Preceding and/or succeeding processing steps relative to the storage of intermediates are hostile (i.e. high temperature, high/low pH and/or high solvent content) to microbial viability - **bioload reduced before or after storage**
1	Intermediates packaged using a closed system or in a controlled environment – **reduced opportunity for addition to bioload**

Example: The intermediate is stored wet with water but the manufacturing process before storage and/or after storage is hostile and packaging is performed in a closed system. Subtract 3 (2 + 1) from the factor "8" to get an adjusted probability factor of 5.

Appendix II [3]

(The table below can be used to determine whether or not the attributes of an isolated intermediate stored wet are favorable for microbiological proliferation.)

Starting material or intermediate was derived synthetically or derived from plant, animal, fermentation, or bioconversion and has been through an extraction into a water immiscible solvent.		Starting material or intermediate was derived from plant, animal, fermentation, or bioconversion and has not been through an extraction into a water immiscible solvent.	
Attribute of wet intermediate	**Yes/No**	**Attribute of wet intermediate**	**Yes/No**
Water activity (a_w) value is <0.60 [2]		Water activity (a_w) value is <0.60 [2]	
pH < 3		pH < 2	
pH > 10		pH > 10	
Methanol > 40% relative to water		Methanol > 50% relative to water	
Other Alcohols > 20% relative to water		Other Alcohols > 40% relative to water	
THF > 30% relative to water		THF > 30% relative to water	
Acetone > 30% relative to water		Acetone > 30% relative to water	
Wet with a water immiscible solvent		Wet with a water immiscible solvent	
If the answer is Yes for any of the attributes above then the wet intermediate can be considered to be held under conditions unfavorable for microbiological proliferation. If the answer is No for all the attributes above, then the wet intermediate should be considered to be held under conditions favorable for microbiological proliferation.			

